ORIGINAL ARTICLE

Increasing the Potassium Level in Patients at High Risk for Ventricular Arrhythmias

Christian Jøns, M.D., Ph.D.,[1,2] Chaoqun Zheng, M.D.,[1] Ulrik C.G. Winsløw, M.D., Ph.D.,[1] Elisabeth M. Danielsen, M.D.,[1] Tharsika Sakthivel, M.D.,[1] Emil A. Frandsen, M.D.,[1] Hillah Saffi, M.D.,[1] Sadjedeh S. Vakilzadeh-Hashemi, M.D.,[1] Ketil J. Haugan, M.D., Ph.D.,[3] Niels E. Bruun, M.D., D.M.Sc.,[2,3] Kasper K. Iversen, M.D., D.M.Sc.,[2,4] Helle S. Bosselmann, M.D., Ph.D.,[3] Niels Risum, M.D., Ph.D.,[1] and Henning Bundgaard, M.D., D.M.Sc.,[1,2] for the POTCAST Study Group

ABSTRACT

BACKGROUND

Hypokalemia and even low-normal plasma potassium levels increase the risk of ventricular arrhythmias among patients with cardiovascular disease. An assessment of a strategy of actively increasing plasma potassium levels to the high-normal range is needed.

METHODS

In this multicenter, open-label, event-driven, randomized superiority trial conducted in Denmark, we enrolled participants at high risk for ventricular arrhythmias (defined as those with an implantable cardioverter–defibrillator [ICD]) and with a baseline plasma potassium level of 4.3 mmol per liter or lower. Participants were randomly assigned, in a 1:1 ratio, to a treatment regimen aimed at increasing the plasma potassium level to a high-normal level (4.5 to 5.0 mmol per liter) by means of potassium supplementation, a mineralocorticoid receptor antagonist, or both plus dietary guidance and standard care (high-normal potassium group) or to standard care only (standard-care group). The primary end point was a composite of documented sustained ventricular tachycardia or appropriate ICD therapy, unplanned hospitalization (>24 hours) for arrhythmia or heart failure, or death from any cause, assessed in a time-to-first-event analysis.

RESULTS

Among the 1200 participants who underwent randomization (600 assigned to each group), the median duration of follow-up was 39.6 months (interquartile range, 26.4 to 49.3). A primary end-point event occurred in 136 participants (22.7%; 7.3 events per 100 person-years) in the high-normal potassium group, as compared with 175 participants (29.2%; 9.6 events per 100 person-years) in the standard-care group (hazard ratio, 0.76; 95% confidence interval, 0.61 to 0.95; P=0.01). The incidence of hospitalization for hyperkalemia or hypokalemia was similar in the two groups.

CONCLUSIONS

Among participants with any cardiovascular disease who had an ICD and were at high risk for ventricular arrhythmias, a treatment-induced increase in plasma potassium levels led to a significantly lower risk of appropriate ICD therapy, unplanned hospitalization for arrhythmia or heart failure, or death from any cause than standard care. (Funded by the Independent Research Fund Denmark and others; POTCAST ClinicalTrials.gov number, NCT03833089.)

Author affiliations are listed at the end of the article. Henning Bundgaard can be contacted at henning.bundgaard@regionh.dk or at the Department of Cardiology, the Heart Center, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.

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Potassium plays a pivotal role in the electrical and mechanical function of the heart, and a U-shaped relationship has been observed between plasma potassium levels and death.[1] Among patients with cardiovascular disorders, mortality is higher among persons with plasma potassium levels between 3.5 and 4.0 mmol per liter (normal range, 3.5 to 5.0), and plasma potassium levels in the high-normal range (4.5 to 5.0 mmol per liter) are associated with lower mortality.[2]

Among patients with heart failure, mineralocorticoid receptor antagonists and angiotensin-converting–enzyme inhibitors reduce the risk of death, including the risk of sudden death from cardiac causes,[3,4] as well as the incidence of atrial fibrillation.[5-7] Both drug classes increase plasma potassium levels and reduce the risk of hypokalemia.[8,9] A randomized trial showed that among persons at increased risk for cardiovascular events, the substitution of part of the dietary sodium chloride intake with potassium chloride lowered the incidence of cardiovascular events, including death from any cause.[10]

Clinical awareness regarding management of overt hypokalemia or hyperkalemia is high, but guidelines have not addressed the potential benefit of increasing plasma potassium levels to the high-normal range.[11,12] Such an increase may protect against arrhythmia caused by episodes of hypokalemia.[13] A wide range of cardiac diseases may be complicated by malignant ventricular arrhythmias that may cause syncope or sudden cardiac death.[12] Strategies to reduce ventricular arrhythmias remain a critical unmet need.

The POTCAST (Targeted Potassium Levels to Decrease Arrhythmia Burden in High-Risk Patients with Cardiovascular Diseases) trial was designed to assess the efficacy and safety of a treatment-induced increase in plasma potassium levels targeting high-normal levels through dietary guidance, potassium supplementation, or treatment with a mineralocorticoid receptor antagonist in participants at high risk for ventricular arrhythmias. We categorized patients as being at high risk for ventricular arrhythmias if they had an implantable cardioverter–defibrillator (ICD), irrespective of the cause or type of heart disease.

Methods

Trial Design and Oversight

The POTCAST trial was an investigator-initiated, multicenter, open-label, event-driven, randomized superiority trial, as described previously.[14] Participants were enrolled consecutively at three centers in Denmark at which ICDs were implanted. The trial was designed and overseen by a steering committee with representatives from all three centers (additional information is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). Potential clinical events and adverse events were assessed by an end-point committee consisting of members of the steering committee, and any event that was classified as a potential component of the composite primary end point was adjudicated by an external adjudication committee, which comprised two independent specialists in cardiac electrophysiology and device interrogation who were unaware of the group assignments. Data analyses were conducted by the investigators. The trial protocol and statistical analysis plan are available at NEJM.org.

The trial was supported by unrestricted grants from the Independent Research Fund Denmark, the Danish Heart Foundation, and the Novo Nordisk Foundation. The funders had no influence on the design or conduct of the trial, the collection or analysis of the data, the interpretation of results, or the drafting or editing of the manuscript. The protocol was approved by the ethics committee for the Capital Region of Denmark, and the trial was conducted in accordance with the principles of the Declaration of Helsinki. All the authors had access to the data, participated in the preparation of the manuscript, and made the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the first and last authors without external assistance. The trial was investigator-driven, and there were no confidentiality agreements.

Trial Participants

Adults 18 years of age or older were eligible to enroll in the trial if they had an ICD or a cardiac-

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resynchronization therapy defibrillator (CRT-D) and had a baseline plasma potassium level of 4.3 mmol per liter or lower. Persons were excluded if the estimated glomerular filtration rate (eGFR) was less than 30 ml per minute per 1.73 m^2 of body-surface area, if they were pregnant, or if they lacked the ability to understand and sign the consent form. All the participants provided written informed consent.

TRIAL PROCEDURES

The participants were randomly assigned, in a 1:1 ratio, to receive treatment to increase the plasma potassium level in addition to standard care (high-normal potassium group) or to receive standard care only (standard-care group). Appropriate treatment in accordance with society guidelines was ensured for all the participants. All the participants in the high-normal potassium group received written information on a potassium-rich diet and initiated trial medication with potassium supplements, administered as potassium chloride tablets (750 mg [approximately 10 mmol]), a mineralocorticoid receptor antagonist, or both to reach the target plasma potassium level of 4.5 to 5.0 mmol per liter. The maximum daily doses for the mineralocorticoid receptor antagonists were 100 mg for spironolactone and 50 mg for eplerenone; the maximum daily dose for potassium chloride was 4.5 g. If possible, doses of thiazides and loop diuretics were reduced or discontinued. Participants attended visits every other week for blood tests and blood-pressure measurement to evaluate whether increases were needed in the potassium supplement medications and for assessment of adherence and potential side effects (further details are provided in the Supplementary Appendix).

After adjustment of treatment, the participants had follow-up visits every 6 months. The trial medication was adjusted only if the plasma potassium level was greater than 5.0 mmol per liter, with confirmation on a second blood test, or if the participant reported unacceptable side effects. The treatment was continued until the end of the trial (March 31, 2025). The observation period was the time from randomization until the trial ended, the participant withdrew, or the participant died.

TRIAL END POINTS AND SAFETY MEASUREMENTS

The primary end point was a composite of sustained ventricular tachycardia with a rate of more than 125 beats per minute lasting more than 30 seconds, as documented by electrocardiography (ECG) or observed on the ICD cardiac electrogram; any appropriate ICD therapy, as documented by ECG or on the ICD cardiac electrogram; any unplanned hospitalization for more than 24 hours for arrhythmia or heart failure and leading to a change in drug or invasive treatment; or death from any cause during the trial period (in a time-to-first-event analysis). Secondary end points reported here include death from any cause, hospitalization for heart failure, hospitalization for cardiac arrhythmias, hospitalization for kidney failure or electrolyte disturbances, hospitalization for supraventricular arrhythmias, any appropriate ICD therapy, and inappropriate ICD therapy (other secondary end points are not reported here). Safety measurements included hypokalemia and hyperkalemia, changes in plasma creatinine levels, hospitalization for other cardiovascular causes, hospitalization for noncardiovascular causes, hospitalization for any cause, and a composite of hospitalization for any cause or death.

STATISTICAL ANALYSIS

The trial was designed to have 80% power to detect a 28% lower risk of a primary end-point event in the high-normal potassium group than in the standard-care group, with the assumption that increasing plasma potassium levels to high-normal levels would result in a 40% lower incidence of primary end-point events but that 30% of the participants in the high-normal potassium group would not have potassium levels that reached the target range. This assumption would result in an annual rate of a primary end-point event of 11.5% in the high-normal potassium group and 16% in the standard-care group. At least 291 primary end-point events would be needed for the trial results to be conclusive. The trial initially planned to enroll 1000 participants, but the number was increased to 1200 participants during the latter half of the trial owing to an unexpected decrease in event rates.

The primary end point was analyzed in the intention-to-treat population with the use of time-to-first-event methods. Differences in risks be-

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tween the groups were analyzed with the Cox proportional-hazards model. Since death from any cause was part of the primary end point, no adjustment for competing risk was made. Assumption of proportional hazards was assessed with the log-rank test and was fulfilled. The statistical analysis plan did not include a correction for multiplicity. Except for the primary end point, the efficacy end points were reported as point estimates not adjusted for multiplicity and 95% confidence intervals, and the intervals should not be used in place of hypothesis testing. A Kaplan–Meier plot was used to illustrate the probability of survival without a primary end-point event over time. A forest plot of the primary end point was constructed for relevant subgroups, including those defined according to age, sex, ischemic or nonischemic heart disease, heart failure, plasma potassium levels, and primary or secondary prevention as the indication for the ICD. Missing values for plasma potassium and creatinine levels were assessed by imputing missing measurements with the highest and lowest values measured in any participant during the trial. Continuous variables were reported as the means with standard deviations or medians and interquartile ranges, as appropriate, and categorical variables were reported as frequencies and percentages. Event rates were reported as events per 100 person-years. A two-sided P value of less than 0.05 was considered to be statistically significant. Analyses were performed with SAS, version 9.4 (SAS Institute), and R statistical software, version 4.4.2 (R Project for Statistical Computing).

RESULTS

PARTICIPANTS

From March 2019 through September 2024, a total of 1200 participants underwent randomization, with 600 participants randomly assigned to each group (Fig. S1 in the Supplementary Appendix). The mean age of the participants was 62.7±12.0 years, and 19.8% were women. ICD implantation was performed for primary prevention in 43.3% of the participants. The majority of the participants (64.6%) had a history of heart failure, and half the participants had a history of ischemic heart disease. The other half had cardiomyopathies or primary arrhythmia disorders. At baseline, the mean plasma potassium level was 4.01±0.24 mmol per liter (Table 1, Table S1, and Fig. S2). The median duration of follow-up was 39.6 months (interquartile range, 26.4 to 49.3). Missing values for baseline characteristics, ICD data, and hospitalization were very rare.

INCREASE IN PLASMA POTASSIUM LEVELS

A total of 572 of 600 participants (95.3%) completed the drug-adjustment process. Of these, 222 participants were receiving a mineralocorticoid receptor antagonist at baseline and an additional 181 participants started receiving a mineralocorticoid receptor antagonist. After initiation failed in 4 participants, 399 were receiving a mineralocorticoid receptor antagonist at the end of the drug-adjustment period and 73 participants received it as the only trial medication. A total of 131 participants were receiving potassium supplementation at baseline and 343 participants started receiving potassium supplementation. At the end of the drug-adjustment period, 474 participants were receiving potassium supplementation and 148 participants were receiving it as the only trial medication (Table S2).

The levels of plasma potassium reached the target range (4.5 to 5.0 mmol per liter) in a total of 249 participants (Fig. S2). The most common reasons that plasma potassium levels did not reach the target range were that a participant had received the maximum tolerated dose (146 participants [25.5%]), declined to take more medications (71 participants [12.4%]), had reached the maximum daily dose of the trial drugs that was allowed by the protocol (52 participants [9.1%]), or had other reasons (54 participants [9.4%]).

Plasma potassium levels increased from a mean of 4.01±0.24 mmol per liter at baseline to 4.36±0.36 mmol per liter after a median adjustment period of 85 days (interquartile range, 58 to 119) in the high-normal potassium group, as compared with an increase from a mean of 4.01±0.24 mmol per liter at baseline to 4.05±0.33 mmol per liter after 6 months in the standard-care group (Fig. S3A). A total of 451 participants (75.2%) were adherent to the trial regimen until they died or the trial ended. The reasons for discontinuation of the trial regimen are shown in Table S3A.

END POINTS

A primary end-point event occurred in 136 participants (22.7%; 7.3 events per 100 person-years) in the high-normal potassium group, as compared

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Table 1. Characteristics of Participants at Baseline.*

Characteristic	High-Normal Potassium (N=600)	Standard Care (N=600)
Age — yr	62.7±12.1	62.8±11.8
Male sex — no. (%)	483 (80.5)	480 (80.0)
ICD for secondary prevention — no. (%)	346 (57.7)	334 (55.7)
Median left ventricular ejection fraction (IQR) — %	45 (35–55)	45 (30–55)
Left ventricular ejection fraction ≤40% — no. (%)	256 (42.7)	256 (42.7)
NYHA class — no. (%)		
I	353 (58.8)	354 (59.0)
II	213 (35.5)	214 (35.7)
III	34 (5.7)	32 (5.3)
IV	0	0
Plasma potassium level — mmol/liter	4.01±0.24	4.01±0.24
History of ischemic heart disease — no. (%)†		
Ischemic heart disease	293 (48.8)	302 (50.3)
Previous myocardial infarction	208 (34.7)	227 (37.8)
Nonischemic cardiomyopathy and primary arrhythmia — no. (%)†		
Dilated cardiomyopathy	111 (18.5)	90 (15.0)
Nonischemic heart failure, unknown phenotype	40 (6.7)	61 (10.2)
Arrhythmogenic ventricular cardiomyopathy	36 (6.0)	36 (6.0)
Hypertrophic cardiomyopathy	32 (5.3)	34 (5.7)
Primary arrhythmia‡	75 (12.5)	74 (12.3)
Other diagnoses§	23 (3.8)	21 (3.5)
History of heart failure or atrial fibrillation — no. (%)		
Heart failure	390 (65.0)	385 (64.2)
Atrial fibrillation	199 (33.2)	191 (31.8)
History of ventricular tachyarrhythmias		
Previous ventricular tachycardia — no. (%)	414 (69.0)	390 (65.0)
Previous appropriate ICD therapy — no. (%)	181 (30.2)	160 (26.7)
Median time since last ICD therapy (IQR) — days	800 (271–1990)	631 (230–1714)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ICD denotes implantable cardioverter–defibrillator, and NYHA New York Heart Association.
† A small percentage of participants had more than one cardiac diagnosis.
‡ Primary arrhythmia includes long QT syndrome, short QT syndrome, the Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular arrhythmia.
§ This category includes but is not limited to tetralogy of Fallot, Emery–Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, myotonic dystrophy, and coronary-artery vasospasm (formerly called Prinzmetal's angina).

with 175 participants (29.2%; 9.6 events per 100 person-years) in the standard-care group (hazard ratio, 0.76; 95% confidence interval [CI], 0.61 to 0.95; P=0.01) (Table 2, Fig. 1A, and Table S4). The difference between the groups at 5 years was 7.7 percentage points, and the number needed to treat to prevent one event in this population was 12.3 persons (95% CI, 2.0 to 14.0). The effect appeared to be consistent across the prespecified subgroups (Fig. 2). The intervention effect did not appear to differ between the 409 participants who received mineralocorticoid receptor antagonists at the end of the adjustment period (hazard ratio, 0.75; 95% CI, 0.58 to 0.97) and the 191 participants who did not receive mineralocorticoid receptor antagonists (hazard ratio, 0.77; 95% CI,

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Table 2. Primary and Secondary End Points and Safety Measurements.*

End Point or Measurement	High-Normal Potassium (N=600)		Standard Care (N=600)		Hazard Ratio (95% CI)	P Value
	no. of participants with event (%)	*events per 100 person-years*	*no. of participants with event (%)*	*events per 100 person-years*		
Primary composite end point	136 (22.7)	7.30	175 (29.2)	9.60	0.76 (0.61–0.95)	0.01
Components of the primary end point†						
Appropriate ICD therapy or documented ventricular tachycardia	92 (15.3)	5.05	122 (20.3)	6.69	0.75 (0.57–0.98)	—
Death from any cause	34 (5.7)	1.86	41 (6.8)	2.25	0.85 (0.54–1.34)	—
Hospitalization for cardiac arrhythmia	40 (6.7)	2.19	64 (10.7)	3.51	0.63 (0.42–0.93)	—
Hospitalization for heart failure	21 (3.5)	1.15	33 (5.5)	1.81	0.64 (0.37–1.11)	—
Other secondary end points						
Hospitalization for ventricular arrhythmias	31 (5.2)	1.70	41 (6.8)	2.25	0.76 (0.48–1.22)	—
Hospitalization for supraventricular arrhythmias	12 (2.0)	0.66	27 (4.5)	1.48	0.45 (0.23–0.89)	—
Inappropriate ICD therapy	28 (4.7)	1.54	30 (5.0)	1.65	0.95 (0.57–1.60)	—
Hospitalization for electrolyte disturbances or kidney failure	17 (2.8)	0.93	10 (1.7)	0.55	1.75 (0.80–3.82)	—
Safety measurements						
Hospitalization for other cardiovascular causes	35 (5.8)	1.92	31 (5.2)	1.70	1.15 (0.71–1.87)	0.56
Hospitalization for noncardiovascular causes	111 (18.5)	6.09	127 (21.2)	6.96	0.88 (0.68–1.14)	0.34
Hospitalization for any cause	168 (28.0)	9.21	190 (31.7)	10.42	0.88 (0.71–1.08)	0.21
Hospitalization for any cause or death	177 (29.5)	9.71	199 (33.2)	10.91	0.88 (0.72–1.08)	0.22

* Shown are the results for the primary composite end point, the components of the primary and secondary end points, and safety measurements during the trial period. The primary composite end point was the first occurrence of any component of the end point (sustained ventricular tachycardia >125 bpm lasting >30 seconds, documented by electrocardiography [ECG] or on the ICD cardiac electrogram; any appropriate ICD therapy documented by ECG or on the ICD cardiac electrogram; any unplanned hospitalization >24 hours due to arrhythmia or heart failure leading to a change in drug or invasive treatment; or death from any cause during the trial period).

† Each component of the primary composite end point was also a prespecified secondary end point.

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0.56 to 1.00) or between the 249 participants whose plasma potassium levels reached the target range of 4.5 to 5.0 mmol per liter (hazard ratio, 0.84; 95% CI, 0.63 to 1.12) and the 351 participants whose levels did not reach the target range (hazard ratio, 0.70; 95% CI, 0.53 to 0.92).

Appropriate ICD therapy or documented ventricular tachycardia occurred in 92 participants (15.3%) in the high-normal potassium group and in 122 participants (20.3%) in the standard-care group (hazard ratio, 0.75; 95% CI, 0.57 to 0.98). Death from any cause occurred in 34 participants (5.7%) in the high-normal potassium group and in 41 participants (6.8%) in the standard-care group (hazard ratio, 0.85; 95% CI, 0.54 to 1.34). Unplanned hospitalization for cardiac arrhythmias occurred in 40 participants (6.7%) in the high-normal potassium group and in 64 (10.7%) in the standard-care group (hazard ratio, 0.63; 95% CI, 0.42 to 0.93), and unplanned hospitalization for heart failure occurred in 21 participants (3.5%) and 33 participants (5.5%), respectively (hazard ratio, 0.64; 95% CI, 0.37 to 1.11) (Fig. 1 and Table 2). A total of 17 hospitalizations among 17 participants in the high-normal potassium group occurred for hypokalemia (1 participant), hyperkalemia (7 participants), or kidney failure (9 participants) as compared with 12 hospitalizations among 10 participants in the standard-care group for hypokalemia (4 participants), hyperkalemia (2 participants) or kidney failure (6 participants) (hazard ratio, 1.75; 95% CI, 0.80 to 3.82). Other secondary end points are shown in Table 2.

SAFETY MEASUREMENTS

There were no deaths related to the trial regimen. At the end of the trial, the mean between-group difference in plasma creatinine levels was 4.11±1.33 μmol per liter (P=0.002) (Fig. S3B). During the trial period, a total of 802 hospitalizations occurred among 358 participants — 372 hospitalizations among 168 participants in the high-normal potassium group and 430 hospitalizations among 190 participants in the standard-care group. The predominant cause of hospitalization is shown in Table S5. An unplanned hospitalization lasting more than 24 hours or death from any cause occurred in 177 participants (29.5%) in the high-normal potassium group and in 199 participants (33.2%) in the standard-care group (hazard ratio, 0.88; 95% CI, 0.72 to 1.08; P=0.22). Post hoc analyses of changes in the PR, QRS, and corrected QT intervals are shown in Figure S4; changes in right ventricular pacing in participants with an ICD and in left ventricular pacing in participants with a CRT-D device are shown in Figure S5.

DISCUSSION

The results of the POTCAST trial showed that among participants who were at high risk for ventricular arrhythmias (defined as those with an ICD), a dietary and treatment-induced mean increase in plasma potassium levels of approximately 0.3 mmol per liter was associated with a significantly lower risk of a composite end-point event — sustained ventricular tachycardia with a rate of more than 125 beats per minute lasting more than 30 seconds, appropriate ICD therapy, unplanned hospitalization for more than 24 hours due to arrhythmia or heart failure leading to a change in medical or invasive treatment, or death from any cause — than standard care. Among the components of the primary end point, ICD therapy (shock therapy or antitachycardia pacing) or documented ventricular tachycardia appeared to account for the majority of events. The effects of increasing the plasma potassium level seemed consistent across the prespecified subgroups and did not appear to be related to the type of trial drugs used to increase the potassium level or to whether the participants were receiving treatment with a mineralocorticoid receptor antagonist at baseline.

Several placebo-controlled landmark trials of administration of mineralocorticoid receptor antagonists in patients with heart failure have shown improved survival outcomes, including a reduced risk of sudden death from cardiac causes and a reduced risk of worsening heart failure. In the RALES trial (Randomized Aldactone Evaluation Study)[9] involving 1663 patients with severe heart failure, spironolactone treatment increased the mean serum potassium level by 0.3 mmol per liter, a change that was not believed to be clinically important. Findings in EPHESUS (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study),[15] which included 6632 patients, EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure),[16] which included 2737 patients, and FINEARTS-HF (Finerenone Trial to

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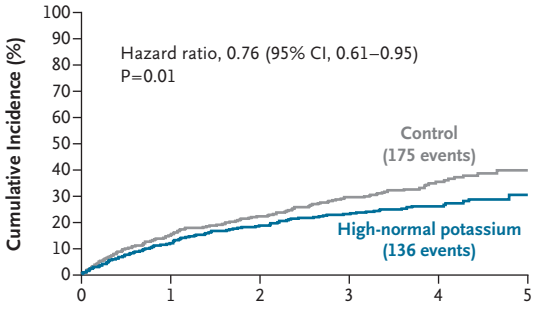
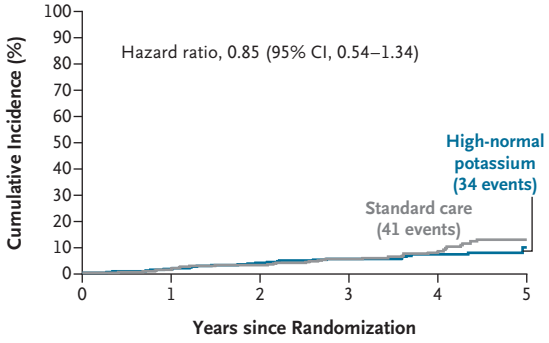
A Primary Composite End Point



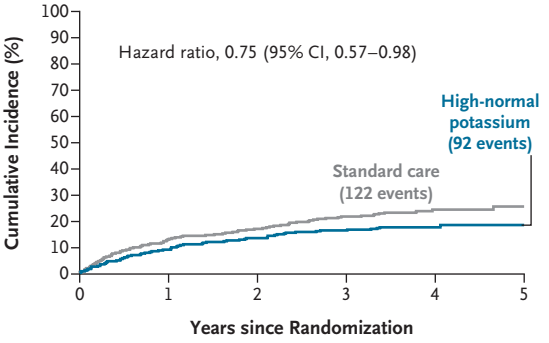
No. at Risk						
Standard care	600	443	371	254	121	34
High-normal potassium	600	452	386	277	131	34

B Death from Any Cause



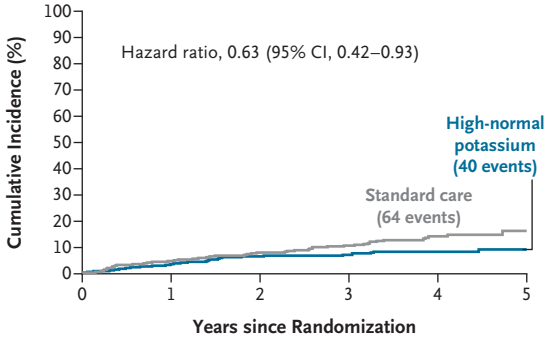
No. at Risk						
Standard care	600	518	467	345	175	48
High-normal potassium	600	507	456	338	166	45

C Appropriate ICD Therapy and Ventricular Tachycardia



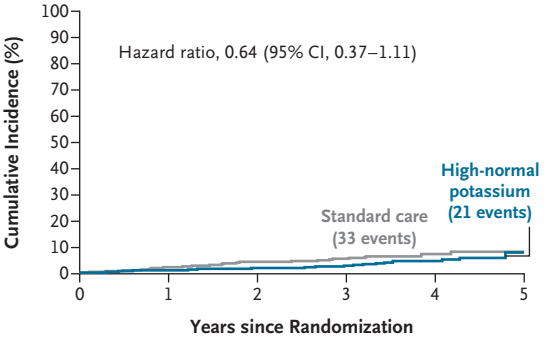
No. at Risk						
Standard care	600	451	388	272	134	38
High-normal potassium	600	462	396	287	138	37

D Hospitalization for Cardiac Arrhythmia



No. at Risk						
Standard care	600	494	434	312	152	41
High-normal potassium	600	490	430	318	153	40

E Hospitalization for Heart Failure



No. at Risk						
Standard care	600	509	451	332	166	47
High-normal potassium	600	504	451	331	158	41

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Figure 1 (facing page). Time-to-First-Event End Points.
Cumulative-incidence plots are shown for the primary composite end point (Panel A) and for its components — death from any cause (Panel B); appropriate implantable cardioverter–defibrillator (ICD) therapy or ventricular tachycardia with a rate of more than 125 beats per minute lasting more than 30 seconds, documented by electrocardiography (ECG) or the ICD cardiac electrogram (Panel C); hospitalization for cardiac arrhythmia (Panel D); and hospitalization for heart failure (Panel E). The two-sided P value is shown for the primary composite end point. The x axis is truncated at 5 years because of the limited number of participants in the trial after that time point. For the individual components of the primary end point, there was no adjustment for multiplicity, and the widths of the confidence intervals should not be used to infer treatment effect.

Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure),[17] which included 6001 patients, showed serum potassium levels that were 0.1 to 0.23 mmol per liter higher in the intervention groups than in the placebo groups. In these landmark trials, the focus was on safety aspects of the higher serum potassium levels induced by mineralocorticoid receptor antagonists, although deaths due to hyperkalemia were not reported in any of the trials.

The findings in the POTCAST trial suggest that part of the observed positive outcome of mineralocorticoid receptor antagonist treatment in the former trials might have been related to the increase in plasma potassium levels, rather than being a side effect. In the POTCAST trial, the positive effect of increasing plasma potassium levels was seen in participants with heart failure as well as in the approximately 40% of participants without heart failure. The increase in plasma potassium levels induced by other widely used drug classes in cardiology, such as beta-adrenergic receptor antagonists[18,19] and inhibitors of the renin–angiotensin–aldosterone axis[8] could possibly also account for some of the beneficial responses to these drugs.

Hyperkalemia is seen mainly in patients with reduced kidney function,[20] and findings in landmark trials have shown that dose reduction and careful monitoring can ensure safety. In addition, the reduced risk of frank hypokalemia is generally agreed to be associated with improved outcomes.[21] In the POTCAST trial, the effect was not dependent on reaching the high-normal plasma potassium target levels, which indicates that the effect of increased plasma potassium levels may relate mainly to avoidance of episodes of low-normal plasma potassium levels or hypokalemia.[2,22]

In the POTCAST trial, the treatment used — dietary guidance, potassium supplementation, a mineralocorticoid receptor antagonist, and, if possible, reductions in potassium-losing diuretics — was inexpensive and available in most health care settings. The target level was reached in less than half the participants, but approximately 3 of every 4 participants received the medication for the duration of the trial.

Human ancestral diets were rich in potassium and low in sodium, with a ratio of up to 10:1, a ratio that has changed markedly to a ratio of less than 1:2 in modern Western diets.[23] A recent meta-analysis involving 10,709 healthy participants showed that higher sodium and lower potassium intakes were dose-dependently associated with a higher cardiovascular risk.[24] Thus, the general population, including patients with cardiovascular diseases, could potentially benefit from higher potassium intake. It should be acknowledged that monitoring of plasma potassium levels may not reflect the more gradual increases over the course of months in total body potassium content in response to increased potassium intake.[25]

This trial had some limitations. First, only patients with an ICD were included, and the effects of increased plasma potassium levels in patients who are at high risk for ventricular arrhythmias but who do not have an ICD cannot be inferred. Second, only patients with an eGFR of at least 30 ml per minute per 1.73 m^2 were included, and in patients treated for episodes of hyperkalemia or with a lower eGFR, the risk of hyperkalemia is higher and high-potassium regimens may not be safe. Third, the POTCAST trial was performed in only one country, and owing to differences in representativeness among populations (Table S6), effects cannot necessarily be inferred for other countries and health care systems. Fourth, the participants were given dietary rec-

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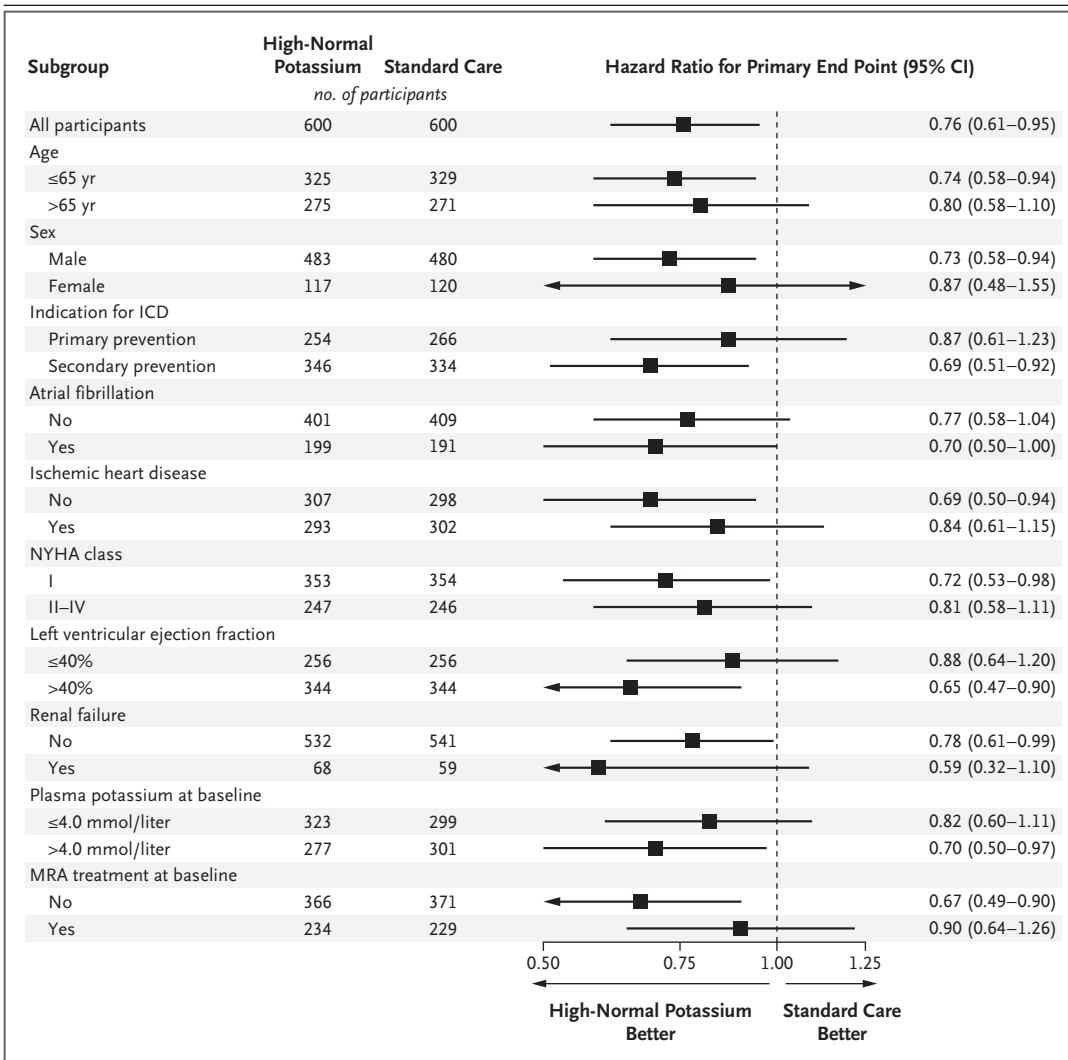

Figure 2. Primary End-Point Results in Prespecified Subgroups.

No adjustment was made for multiplicity, and the widths of the confidence intervals should not be used to infer treatment effects. NYHA denotes New York Heart Association, and MRA mineralocorticoid receptor antagonist.

ommendations to increase the potassium intake. However, adherence to or effects of this recommendation were not accounted for in our trial. Fifth, several of the diagnostic subgroups were small and there was no adjustment for multiplicity, so meaningful disease-specific conclusions cannot be made. Sixth, the trial was not blinded, which may have resulted in bias, but precautions included external adjudication of the components of the primary end point. Finally, the vast majority of the participants were of European descent, and effects in other ethnic groups may be different.

In this open-label, randomized trial involving patients at high risk for ventricular arrhythmias who had an ICD, the treatment-induced increase in plasma potassium levels was superior to standard care in reducing the risk of malignant arrhythmias, hospitalization for heart failure or arrhythmia, or death.

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AUTHOR INFORMATION

[1]Department of Cardiology, Heart Center, Rigshospitalet, University of Copenhagen, Copenhagen; [2]Institute for Clinical Medicine, University of Copenhagen, Copenhagen; [3]Department of Cardiology, Zealand University Hospital — Roskilde, Roskilde, Denmark; [4]Department of Cardiology, Herlev-Gentofte Hospital, University of Copenhagen, Herlev, Denmark.

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